Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments

Part 2: Practical Issues and Specific Cases

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Placebo controls are commonly used in clinical trials of investigational treatments because they have important advantages. In recent years, some have criticized the use of placebo-controlled trials when effective alternative therapy exists, regardless of the expected effect of the therapy. In part 1 of this paper, ethical arguments are addressed and the interpretive problems inherent in the use of active-control equivalence trials to establish efficacy of a new treatment are clarified. However, uncertainties may complicate decisions about appropriate use of placebo controls in some situations. Part 2 discusses more fully the ethical considerations for using placebo controls in particular medical settings. The value and relevance of placebo-controlled trials of new agents in situations in which proven effective therapy is available are also explored.

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In clinical trials conducted in settings where no proven effective therapy exists, the use of placebo controls (or untreated controls, where blinding of therapy is not feasible) is routine and generally uncontroversial. Two concerns about use of placebo controls arise when effective therapy is available (1). An ethical concern is that use of placebos may deny patients potentially helpful treatment. A practical concern is that placebo-controlled trials in this setting may be of little interest or value to patients or investigators and that only a comparison of the new treatment with existing treatment will provide useful data.

In our accompanying paper (2), we concluded that placebo controls are ethical when delaying or omitting available treatment has no permanent adverse consequences for the patient and as long as patients are fully informed about their alternatives. We also showed why such controls are often scientifically necessary. Application of these basic principles, however, is not straightforward in every research situation.

Ethical Acceptability of Placebo Controls

Few would consider problematic the use of placebo-controlled trials to study treatments that relieve minor symptoms or enhance enjoyment of life. Placebo-controlled trials in these situations pose no greater risk than do the regular decisions by many patients and physicians not to use drug therapy in similar circumstances for a wide variety of reasons. In contrast, in the treatment of many serious diseases, consensus would be almost universal that placebo-controlled trials in which some patients would not receive available therapy would be unethical. We do not, for example, omit use of proven therapy in trials of new antiretroviral treatments in patients with AIDS or of new thrombolytics in patients with recent myocardial infarction.

There are other situations, however, in which researchers may disagree about the acceptability or unacceptability of placebo-controlled trials. These can be categorized into several types:

1. Documented evidence of effectiveness of existing therapy is limited to effects on symptoms, but concern exists that treatment may have more important, albeit undemonstrated, long-term effects as well.

2. There is evidence of benefit of long-term treatment on mortality or major morbidity, but the effect of a shorter period of treatment on these outcomes is uncertain.

3. Some evidence of efficacy of the treatment exists but is not universally considered persuasive or sufficient to outweigh the perceived risks.

4. The effective treatment may not be available in many settings, generally because of cost considerations.

Unmeasured Effects on Long-Term Outcomes

The study of new antidepressants illustrates concerns about potentially important but undemonstrated treatment effects. Depression is a well-documented example of a setting in which active control trials are unreliable in assessing efficacy (2–4). Although participants in a given trial might not respond to active agents or might show a good response to

placebo, it can be expected that patients receiving the placebo will have, on average, delayed or decreased relief of depression compared with patients treated with a known active agent.

If a short delay (no more than a few weeks) in relieving symptoms of depression were the only consideration, there should be no ethical objection to placebo-controlled trials of new antidepressants (2). Concern might arise, however, about the possibility of increased risk for suicide in patients receiving placebo (5). Suicide is a rare event in clinical trials because patients deemed at high risk for suicide are excluded from outpatient trials of new antidepressants and trial participants are closely monitored for suicidal thoughts; a small increase in rates would therefore be difficult to detect. An evaluation of almost 2500 patients in placebo-controlled and active-control studies of the popular selective serotonin reuptake inhibitor fluoxetine, however, revealed no increase in suicides or suicide attempts among placebo-treated patients (6). Another review analyzed data on suicide and suicide attempts from all controlled trials of all antidepressants approved for marketing between 1981 and 1997 for which data on these end points were available. This review, which included almost 20 000 patients, found no difference between placebo-treated and drug-treated groups for either outcome (7). Furthermore, a recent review of data on national suicide rates showed no indication that current treatments have reduced rates of suicide in depressed or psychotic patients (8).

Similar issues have arisen with respect to placebo-controlled trials in schizophrenia. Because patients treated for schizophrenia are, on average, more seriously ill than those treated for depression, the level of debate in this area has been more intense (9–12). Even so, a recent comprehensive review concluded that "medication-free" psychotropic research can be conducted safely if appropriate patient selection criteria and monitoring procedures are implemented (13).

One specific criticism of placebo-controlled trials is the need to withdraw effective therapy from patients. Such withdrawal of therapy to allow recurrence of depression, as required before entering a study of a new agent, is not inconsistent with the current practice of withdrawing antidepressant therapy after a period of apparently successful treatment (14). Of course, withdrawal of therapy would be equally necessary in active-control studies if acute antidepressant effects were to be measured in any patients except those with newly diagnosed depression. In addition, although concerns about informed consent in patients with mental or emotional problems are legitimate (15), they are no less relevant to active-control studies (in which patients may receive an ineffective or even harmful experimental therapy) than to placebo-controlled studies.

Short-Term Studies of Treatments with Known Long-Term Benefits

In some cases, the ethical acceptability of placebo controls may depend on aspects of trial design, such as the duration of treatment or the population to be studied. For example, a short-term (for example, 8-week) placebo-controlled trial in patients with mild to moderate hypertension without end-organ damage might be considered acceptable, whereas a longer trial or one that enrolled patients with known hypertensive end-organ damage would be unacceptable. Although the precise length of time for which one can delay treatment without increasing the risk for cardiovascular events is not known, delaying treatment of patients with mild disease for periods at least as long as the typical clinical trial of new agents is consistent with the common practice of following patients with newly diagnosed disease for some months to confirm that hypertension persists. During this time, such nonmedical approaches as weight reduction and increased exercise are generally recommended, even though success rates with these approaches are low compared with medical treatment (16). Nonetheless, although the effect of a short delay in treatment must be small, it is not possible to establish zero risk, and some patients and physicians may even consider this short delay a concern.

Lack of Universally Persuasive Data on Efficacy or Risk–Benefit Ratio

In some cases, identifying "known" effective therapy is not straightforward. A possible approach in the United States might be to use the availability of therapy approved by the U.S. Food and Drug Administration (FDA) for treatment of the condition of interest as the basis for this determination. It should be recognized, however, that FDA marketing approval does not establish treatment as "standard of care," even in the United States and certainly not in other countries. An example is use of tissue plasminogen activator (tPA) in acute ischemic stroke. Tissue plasminogen activator received FDA approval in 1996 on the basis of trials conducted by the National Institute of Neu-

rological Disorders and Stroke demonstrating a decrease in stroke-related disability (17). Even though tPA was the first approved treatment for acute stroke, many physicians remained reluctant to use it, largely because of concerns about increased risk for intracerebral hemorrhage (18, 19). In these circumstances, sponsors, clinical investigators, institutional review boards, and the FDA agreed that placebo-controlled trials of new agents to treat stroke remained appropriate as long as patients were fully informed about tPA as an available treatment option outside the trial. Three years after the reporting of the tPA trials, a large European trial in an overlapping but not identical patient population reported essentially negative results for tPA treatment of acute stroke (20), increasing the uncertainty surrounding risk–benefit considerations for this agent. Thus, even though tPA was approved by the FDA and was the only treatment marketed for acute stroke, placebo-controlled trials of new agents to treat stroke continued to be conducted (21, 22).

International differences exist in the acceptability of available treatments. For example, some trials of second-line treatments for cancer conducted in Europe with untreated controls could not be carried out in the United States (23, 24), reflecting differences in criteria for determining effectiveness of cancer drugs. Tumor response rates that are considered acceptable initial evidence of effectiveness in refractory cancer in the United States (25) would not ordinarily be acceptable to European authorities, who generally have asked for evidence of clinical benefit, such as prolonged survival or symptom relief.

Similar differences in international perspectives have been seen in the field of HIV infection. The Concorde trial (26), a placebo-controlled trial of zidovudine treatment in early HIV infection sponsored by the U.K. Medical Research Council, is a well-known example. This trial continued despite results of U.S. trials that appeared to document at least early benefits of this treatment (27, 28). (The Concorde trial results were ultimately negative, casting some doubt on the value of zidovudine in this setting.) Here, too, differences in the definition of effectiveness (delay of progression to AIDS vs. prolonged survival) influenced judgments about treatment acceptability.

In some cases, even where consensus is widespread that available treatment prolongs life or prevents major morbidity, the treatment may be rejected because of fear of toxicity. Whole-cell pertussis vaccines have been used worldwide for most of the 20th century and their efficacy is undisputed; nevertheless, concerns about side effects reduced their use to very low levels in some countries. Recent trials of new, potentially less toxic, acellular pertussis vaccines conducted in Sweden and Italy therefore used placebo controls (29, 30).

Established therapies may also be challenged when the supporting data were never very strong or when new questions arise. For example, a placebo-controlled trial studied administration of antiarrhythmic agents after myocardial infarction, a use for which these drugs were never approved by the FDA but that was nonetheless common practice in the 1980s. Surprisingly, the study showed that use of antiarrhythmic drugs significantly increased mortality (31). Digoxin, an accepted treatment for congestive heart failure for more than 100 years, was recently studied in a placebo-controlled trial because of questions about its effectiveness and safety. The drug had no effect on survival but did relieve symptoms (32). The effectiveness of the long-standing practice of early fluid replacement in hypotensive persons with penetrating wounds was recently studied in a trial comparing immediate (prehospital) with delayed (in the operating room) fluid resuscitation. The trial found that immediate fluid resuscitation was associated with further bleeding and poorer survival (33).

Accessibility of Proven Treatment

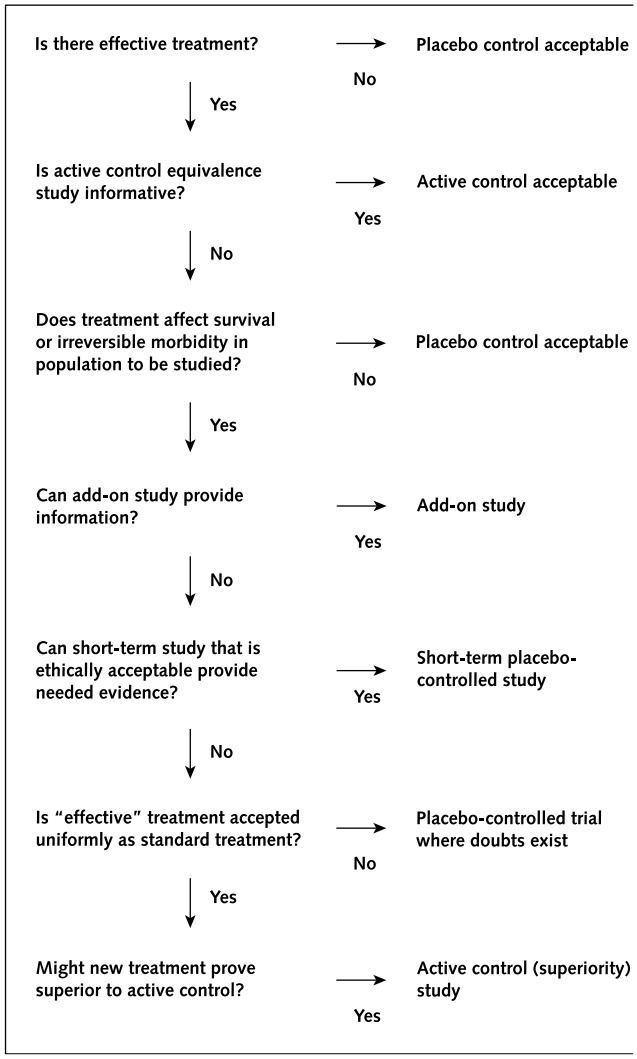
A particularly contentious issue is the use of placebo controls to study new treatments in a population without access to a proven treatment. The ethics of placebo-controlled trials of interventions to prevent perinatal transmission of HIV infection in Asia and Africa, for example, have been widely debated. Some have argued that it is unethical to leave patients untreated when a proven life-saving therapy is in use anywhere in the world (34, 35). Others counter that the appropriate comparison, and the only one of any value to the population under study, is to the current local standard of care (36–40). We note, however, that the conduct of placebo-controlled trials in a developed country that would be considered unethical in another developed country, as described in the previous section, has evoked little of the furor that surrounded the HIV perinatal transmission trials.

As new information develops or as other circumstances change, the acceptability of placebo controls in specific contexts may change as well. Evidence that some treatments for rheumatoid arthritis effectively delay irreversible

progression of disease, for example, has led to increasing interest in designs that permit concomitant use of effective disease-modifying treatments and to reduced trial duration in cases in which use of placebo controls in the absence of other disease-modifying treatments remains appropriate (41, 42).

The **Figure** shows an approach to deciding whether placebo controls are acceptable, accounting for these factors.

Figure. **Considerations for use of placebo controls.**



Patient Decisions To Participate in Placebo-Controlled Trials

Patients may choose not to participate in trials. Reluctance to participate may be greater when there is a placebo control and patients are asked to forgo or delay known effective therapy, but large numbers of patients regularly agree to participate in placebo-controlled trials of new agents. Diverse considerations may enter into a competent and informed person's decision to enter a trial, such as interest in being treated and monitored by the specialists performing the trial, curiosity about the scientific process, lack of enthusiasm for existing therapies, or simple altruism (43). The perceived scientific value of the trial may contribute to this decision (44). Although care must be taken not to permit manipulation of such considerations (for example, by exaggerating the scientific importance of the trial), it seems reasonable to allow potential study participants to balance these types of benefits against the potential risks of participation in the trial.

A longer-range rationale for a patient's participation in a placebo-controlled trial relates to ultimate clinical benefit for that patient. If placebo-controlled trials are needed to reliably identify new effective treatments for the condition under study, the trial participants themselves may benefit in the future, whatever their assigned treatment in the trial. This is a nontrivial consideration in the treatment of such diseases as depression, in which patients frequently try multiple agents before settling on one that they find reasonably satisfactory. Thus, for some patients, forgoing active treatment for the short term may improve their long-term chances of successful treatment.

The Value of Placebo Comparisons in the Setting of Existing Effective Treatment

Those who criticize use of placebo-controlled trials when effective therapy exists have argued that placebo comparisons have no scientific value in this setting because comparison to standard therapy is all that is of interest. It would follow from this view that in a setting where an equivalence design is uninformative, new treatments would need to be proven superior to existing therapy in order to win marketing approval. Such an approach would be extremely detrimental to the public health; many major therapeutic advances have emerged from the availability of drugs that are not more effective than existing agents but have lesser or different toxicity. These drugs would not show superior efficacy in active-control trials, yet equivalence to the active control with respect to efficacy would not have been informative for reasons described in part 1 of this paper (2). Reduced toxicity is clearly of value only when the agent is known to be effective. The **Table** lists

Table. **Examples of Important Therapeutic Advances in Which New Treatment Was No More Effective Than Established Treatment***

Drug Class	Existing Drug	New Agent	Advance
Antidepressants	Tricyclic antidepressants	SSRIs and others	Different (better accepted) side effects
Antipsychotic drugs	Phenothiazines, butyrophenones	Risperidone, olanzapine, quetiapine	Decreased extrapyramidal effects
Antihistamines	Sedating antihistamines	Nonsedating antihistamines	Lack of sedation
Antianginals	Organic nitrates	β-Blockers, calcium-channel blockers	Lack of tolerance
Anti-inflammatory drugs	Nonselective NSAIDs	COX-2–selective NSAIDs	Potential for decreased gastrointestinal bleeding
Antihypertensive drugs	Diuretics, reserpine	Low-dose diuretics, angiotensin-converting enzyme inhibitors, calcium-channel blockers	Elimination of important side effects (hypokalemia and depression)

* COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor.

examples of moderate to major therapeutic improvements in which the new agents are not more effective than existing therapy and for which placebo-controlled trials were needed to establish efficacy.

Even when new agents do not represent clear advances, and apart from economic "competitiveness" considerations (which are beyond the scope of this paper), it is important that multiple effective drugs be available. Drugs do not behave the same way in all persons. Moreover, even within a class, drugs will often differ in toxicity and in pharmacokinetic properties (such as mode of excretion or metabolism, potential drug–drug interactions, and half-life) that may make them more or less appropriate for different persons. The process of finding the optimal treatment for a particular patient is more likely to be successful when multiple therapeutic options exist.

It might be suggested that in these cases, a new drug should be studied only in persons who are known to be unresponsive to the available drug or for whom available therapy is inappropriate. One would then have a study sample for which no treatment was known to be effective, and a placebo-controlled trial would therefore be uncontroversial. In cases in which treatment has an impact on serious morbidity, this may in fact be the only population that could ethically be studied in a placebo-controlled trial. Applied more broadly, however, this approach would make development far more difficult (the size of such a patient population is limited) and would ignore the potential benefit in a wider group of patients of a toxicity profile that may differ from that of the existing treatment. Moreover, problems with drugs in long use may become newly recognized, making the availability of alternatives important. Twenty years ago, for example, drug–drug interactions were not routinely considered during development. In recent years, several widely used agents have been removed from the market because of drug–drug metabolic interactions (for example, mibefridil and terfenadine). When such effects are discovered, it is potentially important to have available other drugs with a range of properties, so that patients who need multiple drugs can find ones that do not interfere with each other or generate unacceptable toxicity when used in combination.

These arguments admittedly become less compelling as the number of treatments available for specific conditions increases. Providing more choices can be important when only 1 or 2 products are available but is less so when 20 products are available. There is no provision in FDA regulations, however, for a policy that would permit new products to be marketed only if they showed some advantage over existing treatments, no matter how large the pool of existing treatments might be.

Conclusions

Current practice is consistent with the premise that placebo-controlled trials are ethically appropriate when patients assigned to placebo risk only temporary discomfort and are fully informed about alternative treatments that may be available to them outside of the trial. We have discussed several factors that are relevant to the acceptability of placebo controls. A critical factor is the potential for unacceptable risks in patients who remain untreated for the required duration of the trial. There are some settings in which experts will disagree about this potential; in such cases, if placebo-controlled trials are ultimately implemented, those who believe that they are inappropriate can choose not to participate. When physicians and patients exercise this option in large numbers, placebo-controlled trials will become unfeasible in that setting, regardless of the scientific considerations or the views of trial sponsors or regulatory authorities.

Important negative consequences would result from uniformly prohibiting placebo-controlled trials in settings in which known effective therapy is available. Because of the interpretative difficulties of active control equivalence trials in many settings, trials of new products using active controls would not be able to provide persuasive evidence of efficacy unless the new treatment proved statistically superior to the active control. This would inevitably mean fewer treatment choices available to patients and a reduced ability to individualize therapy; treatments that are "best" on a group basis are not necessarily best for each individual patient. Finally, it is critical to recognize that a new treatment might represent a major advance without being more effective than alternatives. It will be difficult if not impossible to identify such treatments without studying them in placebo-controlled trials.

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